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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/529,342	CLARKE ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 24 November 2008.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 42-69 is/are pending in the application.

4a) Of the above claim(s) 43,44,53,62,63,67 and 68 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 42,45-52,54-61,64-66 and 69 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 13 April 2000 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claims 42 and addition of claim 69 is acknowledged and has been entered.

2. Claims 42, 45-52, 54-61, 64-66, and 69 are currently under examination.

3. Claims 43-44, 53, 62-63, 67-68 are withdrawn

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 42, 45-47, 51, 52, 54, 58, 61, 64-66 are rejected under 35 U.S.C. 103(a) as being obvious over Cullis et al [US 6,417,326] in view of Smith et al. [US 6,344,436] in light of Subbarao et al. [Subbarao et al., pH dependent bilayer destabilization by an amphipathic peptide, 1987, 26, 2964-2972].

With respect to claims 42, 64, Cullis et al teach the use of fusogenic liposomes containing fusogenic lipopeptides (column 16, lines 25-30), including GALA (column 17, lines 42-43), . Cullis et al specifically teach that pH-sensitive fusogenic polymers which can be incorporated into or covalently attached to liposome vesicles. These pH-sensitive fusogenic polymers trigger fusion or release of the contents of the carrier systems on protonation of the carboxyl groups when the carrier systems encounter an acidic environment (column 25, lines 1-26), which are

sometimes found in tumors (column 31, lines 44-45). Cullis et al teach targeting mechanisms such as monoclonal antibodies specific to antigens associated with neoplasms (column 28, lines 44-50) and require that the targeting agents be positioned on the surface of the liposome in such a manner that the target moieties are available for interaction with the target such as a cell surface receptor (column 29, lines 4-10). Cullis et al further teach the use of a fluorescent marker ANTS for determining the pH-induced destabilization of membranes (column 59, lines 5-20). Cullis et al. fail to teach that the GALA peptide is non-covalently attached to the liposomes.

Smith et al., however, teach peptide-macromolecule complexes for delivering a macromolecule into a cell (see entire document, in particular column 2, lines 62-67), comprising a phospholipid bilayer, receptor ligand for targeting specific cells, and lytic peptides (fig. 1), wherein the lytic peptides disrupts the structural organization of the cell membrane to thereby cause leakage through the endosome into the cytoplasm (column 6, lines 53-65) and which may comprise amphipathic peptides such as GALA (column 7, lines 55-61), wherein the lytic peptides may be associated by covalent or non-covalent means (column 6, lines 45-52, column 8, lines 25-30). Although Smith et al. do not explicitly disclose that GALA interacts with the layer to act as or mediate the opening of pores or channels, one of ordinary skill in the art would have known, as evidenced by Subbarao et al. that GALA are peptides attached to the surface of liposomes and interact with bilayers in a pH-dependent fashion (p.2965, col.1, para.2), wherein when the pH is decreased to pH 5, it would promote helix formation within the bilayer (p. 2970, col.1, para. 2), resulting in pores.

Therefore, Smith shows that covalently and non-covalently attached GALA are equivalent structures known in the art capable of performing the same functions. Therefore,

because these two attachments were art-recognized equivalents at the time the invention was made, one of ordinary skill in the art would have found it obvious to substitute non-covalently attached GALA for covalently attached GALA.

6. With respect to claim 45, Cullis et al. teach that the lipopeptide may be incorporated into outer monolayers of the liposome (column 16, lines 25-33), while as discussed above, Smith et al. disclose that the lytic peptides may be associated by covalent or non-covalent means (column 6, lines 45-52, column 8, lines 25-30)

7. With respect to claims 46-47, Cullis et al teach targeting mechanisms such as monoclonal antibodies specific to antigens associated with neoplasms (column 28, lines 44-50) and require that the targeting agents be positioned on the surface of the liposome in such a manner that the target moieties are available for interaction with the target such as a cell surface receptor (column 29, lines 4-10), and comprise a connector portion which must have both a lipophilic anchor and a hydrophilic reactive group suitable for reacting with the target agents (column 29, lines 15-20).

8. With respect to claims 51-52, Cullis et al teach the use of fusogenic liposomes containing fusogenic lipopeptides (column 16, lines 25-30), including GALA (column 17, lines 42-43).

9. With respect to claim 54, Cullis et al further teach the use of a fluorescent marker ANTS for determining the pH-induced destabilization of membranes (column 59, lines 5-20).

10. With respect to claims 58, 61, Cullis et al teach targeting mechanisms such as monoclonal antibodies specific to antigens associated with neoplasms (column 28, lines 44-50), which are pathogenic cells.

11. With respect to claims 65, 66, Cullis et al. teach that the liposomes are stable at higher pHs, such as 7.5, but destabilize by decreasing the pH below 6.0 (column 16, lines 25-41).

12. Claims 48-50 is rejected under 35 U.S.C. 103(a) as being obvious over Cullis et al [US 6,417,326] in view of Smith et al. [US 6,344,436] in light of Subbarao et al. [Subbarao et al., pH dependent bilayer destabilization by an amphipathic peptide, 1987, 26, 2964-2972], as applied to claim 42 above, and further in view of Bally et al. [US 5,047,245].

With respect to claims 48-50, Cullis et al. and Smith et al. teach the invention as discussed above but fail to teach binding moieties comprising biotin and avidin for aggregating around a cell to be detected.

Bally et al., however, teach providing streptavidin and biotin coupled to liposomes (column 3, lines 15-57), such that aggregation may occur for aggregation type diagnostic assays (column 5, lines 15-30). Bally et al. further teach that this allows for the liposomes to specifically target target cells with little non-specific binding (column 5, lines 30-35).

Therefore, one of ordinary skill in the art at the time of the invention would have found it obvious to have provided binding moieties comprising biotin and avidin for aggregating around a cell to be detected, as this would allow a greater number of liposomes to target and bind to a desired cell.

13. Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis et al [US 6,417,326] in view of Smith et al. [US 6,344,436] in light of Subbarao et al. [Subbarao et al.,

pH dependent bilayer destabilization by an amphipathic peptide, 1987, 26, 2964-2972], as applied to claim 42 above, and further in view of Levinson et al [US 6,020,142].

With respect to claims 55-57, Cullis et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide such as GALA that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type as discussed above. Cullis et al do not teach that the species is an enzyme or a substrate for an enzyme.

Levinson et al, however, teach the use of a delivery complex such as liposomes (column 3, lines 5-12) for delivering enzymes and substrates such as glucose oxidase (column 25, lines 40-42) in order to label RATH gene peptide-specific antibodies. This is important as the RATH1.1 gene product has been demonstrated to act as a mediator of signal transduction events, and and the detection of compounds which modulate the RATH gene product would allow for the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation (column 1, lines 29-62).

Therefore it would have been obvious in the method of Cullis et al to have the liposomes deliver enzymes and substrates such as glucose oxidase, as suggested by Levinson et al, in order to allow for the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation.

14. Claims 59, 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis et al [US 6,417,326] in view of Smith et al. [US 6,344,436] in light of Subbarao et al. [Subbarao et al.,

pH dependent bilayer destabilization by an amphipathic peptide, 1987, 26, 2964-2972], as applied to claims 42 and 58 above, and further in view of Robinson et al [US 5,994,149].

With respect to claim 59, Cullis et al teach the use of lipid particles to detect pathogenic cells, as discussed above. Cullis et al do not teach the detection of pathogenic cells in foodstuffs, or teach the detection of bacteria.

Robinson et al, however, do teach the analysis of foodstuffs for pathogenic cells such as bacteria, viruses, parasites, yeast and molds (column 3, lines 44-51) using liposomes (column 4, lines 19-24). Robinson et al further teach that it would be desirable to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, bacteria, yeasts and molds in a rapid manner (column 3, lines 54-65) as this would allow for the determination of common diseases that are potentially affecting food crops or patients (column 1, line 60 - column 2, line 30, column 7, lines 39-45).

Therefore it would be obvious to teach the detection of pathogenic cells in foodstuffs, as taught by Robinson et al, in the method of Cullis et al, in order to allow for the rapid identification of diseases that are affecting plant crops.

15. With respect to claim 69, Cullis et al. and Smith et al. teach the use of lipid particles to detect pathogenic cells, as discussed above, but do not specifically teach the detection of bacteria.

Robinson et al, however, do teach the analysis of patients for pathogenic cells such as bacteria, viruses, parasites, yeast and molds (column 3, lines 44-51) using liposomes (column 4, lines 19-24). Robinson et al further teach that it would be desirable to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification

of pathogenic fungi, bacteria, yeasts and molds in a rapid manner (column 3, lines 54-65) as this would allow for the determination of common diseases that are potentially affecting patients (column 1, line 60 - column 2, line 30, column 7, lines 39-45).

Therefore it would be obvious to teach the detection of pathogenic cells in foodstuffs, as well as for the detection of bacteria, as taught by Robinson et al, in the method of Cullis et al, in order to allow for the rapid identification of diseases that are affecting a human patient.

16. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis [US 6,417,326] in view of Smith et al. [US 6,344,436] in light of Subbarao et al. [Subbarao et al., pH dependent bilayer destabilization by an amphipathic peptide, 1987, 26, 2964-2972], as applied to claims 42 and 58 above, and further in view of Blondin et al [US 4,808,517].

Cullis et al teach the use of lipid particles to detect pathogenic cells, as discussed above. Cullis et al do not teach the detection of pathogenic cells in water samples.

Blondin et al, however, do teach a method of using of lipid vesicles (column 4, lines 9-24) for the detection of toxins in water samples (column 8, lines 20-32) that is economical and efficient and can be quickly and easily performed (column 2, lines 64-68).

Therefore it would be obvious to use the method of Cullis et al to analyze water samples for pathogens as taught by Blondin et al, in order to detect toxins economically, efficiently, quickly and easily.

Response to Arguments

17. Applicant's arguments with respect to claims 42, 45-52, 54-61, 64-66, and 69 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

18. No claims are allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571)272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nelson Yang/
Patent Examiner, Art Unit 1641